Chemical Research in Toxicology

pubs.acs.org/crt

Editorial

Alan Poland, MS, MD: 1940–2020 Poisons as Probes of Biological Function

Cite This: *Chem. Res. Toxicol.* 2021, 34, 1–4

Read Online

ACCESS | Metrics & More | Article Recommendations

Downloaded via 89.64.124.185 on March 30, 2023 at 11:11:27 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

We lost a great scientific mind on February 20, 2020 with the passing of Alan Poland. Alan's work represents one of the most significant achievements in modern toxicology, the discovery of the Ah receptor and its role in the toxic mechanism of halogenated dioxins and dibenzofurans. His pioneering work, employing these highly toxic molecules as molecular probes of biological function, opened the door to a larger understanding of how animals adapt metabolically to changing chemical and physical environments. Through his foundational research, scientific leadership, and mentoring, we also have greater insights into circadian rhythms, hypoxia signal transduction, and the regulation of xenobiotic metabolism.

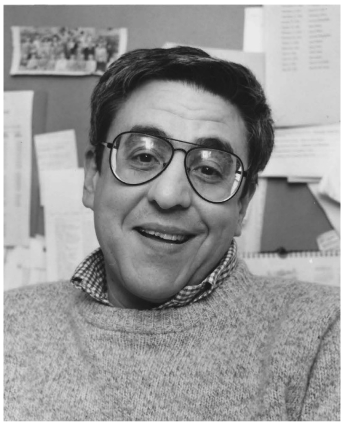

Photo of Prof. Alan Poland. Authorized by Robyn Perrin, Ph.D., University of Wisconsin.

After graduation from Rensselaer Polytechnical Institute in 1961, Alan went on to medical school at the University of Rochester where he spent a year (1963–1964) doing research in the laboratory of Lawrence G. Raisz of the Department of Pharmacology. Larry Raisz was an endocrinologist with an illustrious career in bone metabolism and an early and important influence on Alan's professional life. The Medical School had a program that allowed medical students to take a year off to learn how to carry out research. Alan worked on developing a radioimmunoassay for parathyroid hormone (PTH), and this success produced his first publication: "Hormone Synthesis and Secretion by Rat Parathyroid Glands in Tissue Culture".[1] Alan was also interested in a then newly recognized hormone, calcitonin, and worked on that as well. It was through these early experiences that Alan developed an appreciation for receptor theory and acquired the mathematical ability to describe it. Alan received his MD and MS in Pharmacology from the University of Rochester in 1966.

After a residency at Bellevue Hospital in New York, Alan moved to the Public Health Service at the Center for Disease Control (CDC) in Atlanta (1967–1969). It was at the CDC that Alan developed an interest in dioxin toxicology through work on the induction of delta-aminolevulinic acid synthase (ALAS) by chlorobenzenes with Joyce Goldstein and through related health surveys of workers at a 2,4,5-T plant, finding chloracne and porphyria cutanea tarda.[2,3] He then went on to become a Research Scientist/Assistant Physician at The Rockefeller University in New York City between 1969 and 1971. During this time, he worked in the Laboratory of Attallah Kappas, learning the chick-egg model and focusing on drug metabolism and mechanisms that underlie human porphyrias.[4,5] During this time, Alan also collaborated with Allan Conney, who was at Wellcome Research Laboratories and an expert on the emerging science of enzyme induction in drug metabolism.[6,7]

In 1971, Alan Poland joined the faculty at The University of Rochester, Department of Pharmacology and Toxicology. It was there that he met two important collaborators, Ed Glover, a returning Vietnam veteran who joined his lab as a research scientist, and Andrew Kende, a Professor in the Chemistry Department. During this time, Alan trained two graduate students, William Greenlee and Phillip Teitelbaum.[8−11]

During this period, Alan also developed collaborations with Daniel Nebert at the National Institutes of Health and scientists at The Jackson Laboratory who, along with Paul Thomas at Roche, were developing an understanding of the genetics of enzyme induction in the mouse model. While at Rochester, Alan Poland, with his newfound collaborators, took advantage of his own engineering, biology, and receptor background, generating a series of structural and radiolabeled dioxin analogues to prove the existence of a soluble binding site that became known as the Ah receptor ("dioxin receptor").[12−22]

In 1977, Dr. Poland was recruited to The McArdle laboratory for Cancer Research to work alongside scientists like Elizabeth and James Miller, Van Potter, Henry Pitot, and Howard Temin. There he continued his chemical and genetic

Published: December 21, 2020

ACS Publications

© 2020 American Chemical Society

https://dx.doi.org/10.1021/acs.chemrestox.0c00159

approaches to characterize the Ah locus and also took on a renewed interest in chloracne with scientist Joyce Knutson. Together, Knutson and Poland wrote seminal papers and reviews on dioxin toxicology that still shape our thinking today.[23−28] While at McArdle, Poland again worked with Ed Glover and Andrew Kende to develop ^{125}I-labeled reversible and photoaffinity ligands. These tools allowed the development of competitive binding assays, models for kinetics of ligand binding, and covalent labeling and denaturing purification of the AHR protein 100 000-fold. These led to the determination of the receptor's N-terminal amino acid sequence and the production of the antibodies that were essential in the characterization of AHR across a variety of species.[29−39]

Armed with antibodies, ligands, and protein sequence, the cloning of the AHR cDNA was completed and revealed its identification as a founding member of the bHLH-PAS transcription factor family, ushering in a new understanding of dioxin toxicology and environmental adaptation.[40] This work also allowed a test of the prediction Poland made in the early 1970s, that the Ah locus encoded an "induction receptor" and that the receptor in so-called "non-responsive" mice had a "diminished affinity" for aromatic hydrocarbons. Comparison of Ah receptor cDNAs from responsive and nonresponsive strains revealed a small number of amino acid differences, and one in particular that explains most of the differential sensitivity among mouse strains.[41] The cloning of the AHR led to an explosion of molecular studies in the 1990s and 2000s that provided a detailed understanding of AHR structure and function and explained differences in sensitivity to dioxin-like chemicals across species, strains, populations, and individuals.

Arguably a more important contribution from his work was the molecular model of dioxin signal transduction that was revealed. The model of ligand-induced translocation, receptor dimerization with ARNT (cloned by Oliver Hankinson's team at UCLA) and interaction with genomic enhancers upstream of target P450 genes (with major contributions from the Laboratories of Nebert, Fujii-Kuriyama, Whitlock, Birnbaum, Gonzalez, Safe, Okey, Gasiewicz, Poellinger, and Gustafson) became a model for bHLH-PAS protein signaling in vertebrates. As a measure of the importance of this described paradigm, two of the last three Nobel Prizes have been given for similar solutions of parallel pathways for the PAS signaling proteins that control circadian rhythms and hypoxia signal transduction.[42,43] Alan also shaped the field by training students and postdocs who went on to make important contributions to our understanding of dioxin toxicity and AHR biology including Greenlee, Bradfield, Eltom, Perdew, and Pollenz. Generations of additional scientists still emerge from these laboratories today, all influenced in part by Alan Poland's legacy and approach to science.

When those who knew him were asked to reflect, two themes recurred: his almost intolerant desire to perform the best experiment possible (no matter how difficult) and his ability to make people laugh with his irreverent and precise wit. While often uncompromising, Alan cared deeply about science and especially young scientists, offering examples of his own early version of "responsible conduct in research" to those lucky enough to be entertained by his wisdom interspersed with humor. He especially valued students, postdocs, and young professors with new ideas, often sitting in the front row to catch their seminars with honest excitement. His respect for young scientists was also countered by his almost irreverence for settled science. In one often-recounted story of the 1993 Gordon Conference on Mechanisms of Toxicity, Alan was spotted repeatedly reading the newspaper in the back row during his colleague's presentations. Rather than take offense, the entirety of the conference attendees hid behind and rattled newspapers of their own when it was Alan's turn to present. Alan, respecting the message with a laugh, self-recognition, and a smile, responded with another amazing seminar during which all newspapers soon went down.

Because Alan would start reading his newspaper in any review of settled science, we chose to honor his memory by offering a short recounting of his milestones in Ah receptor biology and then move into a presentation of new ideas we think he would appreciate and challenge. This is our way to say, "Thank you, Alan".

Mele N. Avilla
Christopher A. Bradfield
Ed Glover
Mark E. Hahn orcid.org/0000-0003-4358-2082
Kristen M. C. Malecki
Paula H. Stern
Rachel H. Wilson

■ AUTHOR INFORMATION

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.chemrestox.0c00159

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

Biographies

Mele Avilla is the lead author of the perspective The Ah Receptor: Adaptive Metabolism, Ligand Diversity, and the Xenokine Model. She is currently a Ph.D. candidate in The Molecular and Environmental Toxicology Program at the University of Wisconsin at Madison. As a student in the laboratory of Chris Bradfield, she represents the next generation of scientists influenced by Alan Poland's scientific legacy.

Chris Bradfield trained with Alan in the heydays of AHR purification and cloning. He considers Alan as one of the most influential people in his life and looks forward to pulling up a chair next to him in the great beyond to laugh and argue.

Ed Glover worked alongside Alan for more than 25 years and was his friend for 50 years. He remembers better than anyone the excellence, excitement of the work, and humor of this wonderful scientist.

Mark Hahn. Since his early days in the Toxicology Training Program at the University of Rochester, Mark Hahn has been influenced and inspired by Alan Poland's work. In the 1990s, Mark was fortunate to have the opportunity to collaborate with Alan (and Mark's Woods Hole colleague John Stegeman) on a phylogenetic survey of AHR proteins, which sparked a lasting interest in AHR evolution.

Kristen Malecki. "Alan's legacy lead to some of the most important insights into the biological underpinnings of toxicology that explain human variation and susceptibility to xenobiotics. Dr. Poland also mentored the next generation of mentors who continue to live out his legacy. They have shaped my own career by opening new avenues of scientific inquiry while guiding with incredible patience, intelligence, and integrity. For this, I will always be grateful."

Paula Stern was a postdoc in Larry Raisz's lab at the University of Rochester in 1963 when Alan Poland joined the lab on a "year-out" program from medical school. They were coauthors on Alan's first publication. Paula recalls Alan's dedication to his work and his warmth as a person and notes that they kept in touch over the more than 50 years since.

Rachel Wilson is a Ph.D. candidate in the Laboratory of Chris Bradfield and a Ph.D. candidate in The Molecular and Environmental Toxicology Program at the University of Wisconsin. She continues the legacy of Alan Poland through her genetic studies of AHR biology and its role in normal physiology.

■ REFERENCES

(1) Au, W. Y., Poland, A. P., Stern, P. H., and Raisz, L. G. (1970) Hormone synthesis and secretion by rat parathyroid glands in tissue culture. *J. Clin. Invest. 49* (9), 1639−46.

(2) Poland, A., Goldstein, J. A., Hickman, P., and Burse, V. W. (1971) Reciprocal Relationship between Induction of Delta Aminolevulinic Acid Synthetase and Drug Metabolism Produced by Meta Dichlorobenzene. *Biochem. Pharmacol. 20* (6), 1281.

(3) Poland, A. P., Smith, D., Metier, G., and Possick, P. (1971) A health survey of workers in a 2,4-D and 2,4,5-T plan with special attention to chloracne, porphyria cutanea tarda, and psychologic parameters. *Arch. Environ. Health 22* (3), 316−27.

(4) Poland, A., and Kappas, A. (1971) The metabolism of aminopyrine in chick embryo hepatic cell culture: effects of competitive substrates and carbon monoxide. *Mol. Pharmacol. 7* (6), 697−705.

(5) Mitani, F., Winchester, R. J., Alvares, A. P., Poland, A. P., and Kappas, A. (1971) Interaction of cytochrome P-450 with antibodies raised against a solubilized P-450 preparation from hepatic microsomes. *Mol. Pharmacol. 7* (6), 689−96.

(6) Poland, A., Smith, D., Kuntzman, R., Jacobson, M., and Conney, A. H. (1970) Effect of intensive occupational exposure to DDT on phenylbutazone and cortisol metabolism in human subjects. *Clin. Pharmacol. Ther. 11* (5), 724−32.

(7) Conney, A. H., Welch, R., Kuntzman, R., Chang, R., Jacobson, M., Munro-Faure, A. D., Peck, A. W., Bye, A., Poland, A., Poppers, P. J., Finster, M., and Wolff, J. A. (1971) Effects of environmental chemicals on the metabolism of drugs, carcinogens, and normal body constituents in man. *Ann. N. Y. Acad. Sci. 179*, 155−72.

(8) Greenlee, W. F., and Poland, A. (1978) Improved Assay of 7-Ethoxycoumarin O-Deethylase Activity - Induction of Hepatic Enzyme-Activity in C57bl-6j and Dba-2j Mice by Phenobarbital, 3-Methylcholanthrene and 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin. *J. Pharmacol. Exp. Ther. 205* (3), 596−605.

(9) Greenlee, W. F., and Poland, A. (1979) Nuclear Uptake of 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin in C57bl-6j and Dba-2j Mice - Role of the Hepatic Cytosol Receptor Protein. *J. Biol. Chem. 254* (19), 9814−9821.

(10) Poland, A., Teitelbaum, P., and Glover, E. (1989) [I-125]2-Iodo-3,7,8-Trichlorodibenzo-P-Dioxin-Binding Species in Mouse-Liver Induced by Agonists for the Ah Receptor - Characterization and Identification. *Mol. Pharmacol. 36* (1), 113−120.

(11) Poland, A., Teitelbaum, P., Glover, E., and Kende, A. (1989) Stimulation of Invivo Hepatic-Uptake and Invitro Hepatic Binding of [I-125]2-Iodo-3,7,8-Trichlorodibenzo-P-Dioxin by the Administration of Agonists for the Ah Receptor. *Mol. Pharmacol. 36* (1), 121−127.

(12) Poland, A., and Glover, E. (1973) Chlorinated Dibenzo-P-Dioxins - Potent Inducers of Delta-Aminolevulinic Acid Synthetase and Aryl Hydrocarbon Hydroxylase. 2. Study of Structure-Activity Relationship. *Mol. Pharmacol. 9* (6), 736−747.

(13) Poland, A., and Glover, E. (1973) 2,3,7,8-Tetrachlorodibenzo-P-Dioxin - Potent Inducer of Delta-Aminolevulinic Acid Synthetase. *Science 179* (4072), 476−477.

(14) Poland, A., and Glover, E. (1973) Studies on the mechanism of toxicity of the chlorinated dibenzo-p-dioxins. *Environ. Health Perspect. 5*, 245−251.

(15) Poland, A., and Kappas, A. (1973) Chlorcyclizine N-Demethylase Activity in Chick-Embryo Hepatic Cell-Culture. *Biochem. Pharmacol. 22* (6), 749−758.

(16) Poland, A., and Glover, E. (1974) Comparison of 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin, a Potent Inducer of Aryl-Hydrocarbon Hydroxylase, with 3-Methylcholanthrene. *Mol. Pharmacol. 10* (2), 349−359.

(17) Poland, A. P., Glover, E., Robinson, J. R., and Nebert, D. W. (1974) Genetic Expression of Aryl-Hydrocarbon Hydroxylase-Activity - Induction of Monooxygenase Activities and Cytochrome P1−450 Formation by 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin in Mice Genetically Nonresponsive to Other Aromatic-Hydrocarbon. *J. Biol. Chem. 249* (17), 5599−5606.

(18) Nebert, D. W., Robinson, J. R., Niwa, A., Kumari, K., and Poland, A. P. (1975) Genetic Expression of Aryl-Hydrocarbon Hydroxylase-Activity in Mouse. *J. Cell. Physiol. 85* (2), 393−414.

(19) Niwa, A., Kumaki, K., Nebert, D. W., and Poland, A. P. (1975) Genetic Expression of Aryl-Hydrocarbon Hydroxylase-Activity in Mouse - Distinction between Responsive-Homozygote and Responsive-Heterozygote at Ah-Locus. *Arch. Biochem. Biophys. 166* (2), 559−564.

(20) Poland, A., Glover, E., and Kende, A. S. (1976) Stereospecific, High Affinity Binding of 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin by Hepatic Cytosol - Evidence That Binding Species Is Receptor for Induction of Aryl-Hydrocarbon Hydroxylase. *J. Biol. Chem. 251* (16), 4936−4946.

(21) Poland, A., and Kende, A. (1976) 2,3,7,8-Tetrachlorodibenzo-Rho-Dioxin - Environmental Contaminant and Molecular Probe. *Federation Proceedings 35* (12), 2404−2411.

(22) Poland, A., and Glover, E. (1977) Chlorinated Biphenyl Induction of Aryl-Hydrocarbon Hydroxylase-Activity - Study of Structure-Activity Relationship. *Mol. Pharmacol. 13* (5), 924−938.

(23) Knutson, J. C., and Poland, A. (1980) Keratinization of Mouse Teratoma Cell-Line Xb Produced by "2,3,7,8-Tetrachlorodibenzo-P-Dioxin - an Invitro Model of Toxicity. *Cell 22* (1), 27−36.

(24) Knutson, J. C., and Poland, A. (1980) 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin - Failure to Demonstrate Toxicity in 23 Cultured-Cell Types. *Toxicol. Appl. Pharmacol. 54* (3), 377−383.

(25) Knutson, J. C., and Poland, A. (1982) Response of Murine Epidermis to 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin - Interaction of the Ah and Hr Loci. *Cell 30* (1), 225−234.

(26) Poland, A., and Knutson, J. C. (1982) 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin and Related Halogenated Aromatic-Hydrocarbons - Examination of the Mechanism of Toxicity. *Annu. Rev. Pharmacol. Toxicol. 22*, 517−554.

(27) Knutson, J. C., and Poland, A. (1984) 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin - Examination of Biochemical Effects Involved in the Proliferation and Differentiation of Xb Cells. *J. Cell. Physiol. 121* (1), 143−151.

(28) Poland, A., Knutson, J. C., and Glover, E. (1984) Histologic-Changes Produced by "2,3,7,8-Tetrachlorodibenzo-P-Dioxin in the Skin of Mice Carrying Mutations That Affect the Integument. *J. Invest. Dermatol. 83* (6), 454−459.

(29) Poland, A., Glover, E., Ebetino, F. H., and Kende, A. S. (1986) Photoaffinity-Labeling of the Ah Receptor. *J. Biol. Chem. 261* (14), 6352−6365.

(30) Poland, A., and Glover, E. (1987) Variation in the Molecular Mass of the Ah Receptor among Vertebrate Species and Strains of Rats. *Biochem. Biophys. Res. Commun. 146* (3), 1439−1449.

(31) Bradfield, C. A., Kende, A. S., and Poland, A. (1988) Kinetic and Equilibrium Studies of Ah Receptor-Ligand Binding - Use of (I-125)2-Lodo-7,8-Dibromodibenzo-Para-Dioxin. *Mol. Pharmacol. 34* (2), 229−237.

(32) Bradfield, C. A., and Poland, A. (1988) A Competitive-Binding Assay for 2,3,7,8-Tetrachlorodibenzo-Para-Dioxin and Related Ligands of the Ah Receptor. *Mol. Pharmacol. 34* (5), 682−688.

(33) Perdew, G. H., and Poland, A. (1988) Purification of the Ah Receptor from C57bl/6j Mouse-Liver. *J. Biol. Chem. 263* (20), 9848−9852.

(34) Poland, A., and Glover, E. (1988) Ca-2+-Dependent Proteolysis of the Ah Receptor. *Arch. Biochem. Biophys. 261* (1), 103−111.

(35) Poland, A., and Glover, E. (1990) Characterization and Strain Distribution Pattern of the Murine Ah Receptor Specified by the Ahd and Ahb-3 Alleles. *Mol. Pharmacol. 38* (3), 306−312.

(36) Bradfield, C. A., Glover, E., and Poland, A. (1991) Purification and N-Terminal Amino-Acid-Sequence of the Ah Receptor from the C57bl/6j Mouse. *Mol. Pharmacol. 39* (1), 13−19.

(37) Poland, A., Glover, E., and Bradfield, C. A. (1991) Characterization of Polyclonal Antibodies to the Ah Receptor Prepared by Immunization with a Synthetic Peptide Hapten. *Mol. Pharmacol. 39* (1), 20−26.

(38) Hahn, M. E., Poland, A., Glover, E., and Stegeman, J. J. (1994) Photoaffinity-Labeling of the Ah Receptor - Phylogenetic Survey of Diverse Vertebrate and Invertebrate Species. *Arch. Biochem. Biophys. 310* (1), 218−228.

(39) Pollenz, R. S., Sattler, C. A., and Poland, A. (1994) The Aryl-Hydrocarbon Receptor and Aryl-Hydrocarbon Receptor Nuclear Translocator Protein Show Distinct Subcellular Localizations in Hepa 1c1c7 Cells by Immunofluorescence Microscopy. *Mol. Pharmacol. 45* (3), 428−438.

(40) Burbach, K. M., Poland, A., and Bradfield, C. A. (1992) Cloning of the Ah-Receptor Cdna Reveals a Distinctive Ligand-Activated Transcription Factor. *Proc. Natl. Acad. Sci. U. S. A. 89* (17), 8185−8189.

(41) Poland, A., Palen, D., and Glover, E. (1994) Analysis of the 4 Alleles of the Murine Aryl-Hydrocarbon Receptor. *Mol. Pharmacol. 46* (5), 915−921.

(42) Moslehi, J., and Rathmell, W. K. (2020) The 2019 Nobel Prize honors fundamental discoveries in hypoxia response. *J. Clin. Invest. 130* (1), 4−6.

(43) Sehgal, A. (2018) Flies come through again, period. *J. Clin. Invest. 128* (1), 108−109.